



# Human papillomavirus (HPV) vaccine safety concerning POTS, CRPS and related conditions

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*“Without the possibility of open debate, science simply ceases to exist.”*  
-Jan Vandenbroucke, MD

Dear Editor,

I appreciate the American Autonomic Society’s position statement on HPV vaccines and autonomic disorders and agree with its conclusion that given the existing evidence to date, a causal relationship has not been supported [1]. However, I disagree with the assertion that my case series and those of others from Denmark, Japan, Mexico, Italy and other countries “created fear resulting in decreased vaccination rates” [1]. Case series like these are not written by the authors with the intent of gaining media attention or creating fear. Rather, they are written with the intent of alerting the scientific community about a possible safety signal.

Although the European Medicines Agency concluded in 2015 that there is no link between HPV vaccines and postural tachycardia syndrome (POTS), their conclusion was not based on randomized clinical studies set out to determine the incidence of POTS in HPV-vaccinated versus unvaccinated individuals. While such a study remains to be done, we cannot dismiss the mounting evidence from different countries of patients developing POTS, complex regional pain syndrome (CRPS) and other related conditions after HPV vaccines, given the appropriate temporal association with vaccination and plausible biological mechanism as outlined in the recent review [2].

In the argument for HPV vaccine safety with respect to POTS, CRPS and related conditions, the position statement

relies on three references. The first is a report from the Global Advisory Committee on Vaccine Safety meeting, where, while acknowledging that cases of POTS and CRPS continue to be reported, especially from Denmark and Japan, no causal relationship between HPV vaccines and POTS and CRPS was identified [3]. It is unclear from examining the methodology of that reference how the committee arrived at that conclusion when there has not been a study done to address that question.

The second reference is the study by Arana et al. that found a total of 29 patients with POTS worldwide in the Vaccine Adverse Event Reporting System (VAERS) database between 2006 and 2015 [4]. VAERS is a voluntary reporting system, with only 1–10% of the population filing reports, according to the National Vaccine Information Center [5]. A very low number of confirmed POTS cases found in the VAERS database in the span of 9 years worldwide is obviously an underestimation, considering that the author of this letter has been personally involved in the cases of at least as many patients with post-HPV-vaccination POTS over the years. Failure to capture POTS cases in the VAERS database, coupled with underdiagnosis of POTS by medical professionals and a lack of diagnostic codes for POTS in the United States, would yield very few cases of POTS in the VAERS database as evidenced by Arana’s study, making any conclusions of the true incidence rate of post-HPV-vaccination POTS based on VAERS data unreliable.

The third reference is a study from Finland that was designed to establish the incidence rate of POTS in Finland prior to HPV vaccination as a reference point for future HPV vaccine safety evaluations [6]. The study itself never ascertained the incidence rate of POTS in the vaccinated versus the unvaccinated population, so this study is not particularly relevant to the argument for the HPV vaccine safety record with respect to POTS.

In summary, none of the three studies that the position statement referenced has thoroughly and systematically

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investigated, via prospective randomized controlled studies, whether there is a higher incidence of POTS, CRPS and related conditions in HPV-vaccinated versus unvaccinated individuals, which makes the argument for HPV vaccine safety with respect to POTS, CRPS and related conditions largely unsubstantiated.

Unfortunately, not referenced in the position statement is a study of HPV vaccine adverse events by Chandler et al. In that study, which utilized Vigibase, the WHO international database of suspected adverse drug reactions, a combination of headache and dizziness with either fatigue or syncope was found to be more commonly reported in HPV vaccine reports than in non-HPV vaccine reports for females aged 9–25 years [7]. This disparity remained when results were stratified by age and when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) were excluded. Cluster analysis in that study also revealed additional reports of serious adverse events, including hospitalization, following HPV vaccination that overlapped in signs and symptoms with safety signals for POTS, CRPS and CFS [7].

Much like Guillain-Barré syndrome or acute disseminated encephalomyelitis, POTS, CRPS and other related conditions may occur in certain healthy individuals, possibly with a genetic predisposition toward adverse events, following immunization with HPV vaccines. In the future, identifying those at-risk individuals through genetic testing might be possible as part of personalized medicine, which may lead to a reduction in serious adverse events following vaccination. Until those tests become available, detailed package insert and informed consent serve to acknowledge the possible rare adverse events following vaccination. Including POTS, CRPS and related conditions as part of the informed consent for HPV vaccines rather than denying their occurrence after immunization is a better way to ensure

vaccination compliance and improved HPV vaccination rates in the United States.

## Compliance with ethical standards

**Conflict of interest** Svetlana Blitshteyn has served as a medical expert witness on cases of POTS.

## References

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